Review

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Neurosarcoidosis

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ABSTRACT

Sarcoidosis is an autoimmune multisystemic inflammatory disease characterized by non-caseating granulomatous infection, most commonly involving the lung and lymph nodes. About 5–15% of cases involve the central nervous system (CNS), neurologic involvement in sarcoidosis is in the form of peripheral or central nervous system involvement. Recent years have seen substantial advancements in our understanding of neurosarcoidosis, including updated diagnostic standards and improved methods for treatment. We provide an overview of current developments in the identification and management of neurosarcoidosis in this review.

Keywords: Sarcoidosis, central nervous system, tumor necrosis factor

INTRODUCTION

Sarcoidosis is an autoimmune multisystemic inflammatory disease characterized by non-caseating granulomatous inflammation, most commonly involving the lung and lymph nodes. Its etiology is not known exactly. The prevalence and incidence of the disease may vary geographically and environmentally; it is 1.5 times more common in women than in men. It is especially common between 20-60 years of age. Organ involvement may vary according to age and race. Neurologic involvement in sarcoidosis is in the form of peripheral or central nervous system involvement, its incidence is between 5-10% and its morbidity and mortality are high.[1,2] Neurologic symptoms constitute the initial symptoms in 50-70% of patients with NS.[3] Approximately 10-20% of patients with NS (so-called isolated NS) do not have identifiable systemic sarcoidosis.[4-6] NS usually develops within 2 years after diagnosis (75%).[7]

CLINICAL FEATURES

Central Nervous System

Cranial neuropathy: It develops as a result of granulomatous inflammation of cranial nerve nuclei, fascicles or nerves. It is the most common clinical manifestation of NS. Multiple, consecutive cranial neuropathic involvements should bring neurosarcoidosis to mind. It shows a subacute, progressive course. The most commonly affected nerves are the optic, facial and vestibulocochlear nerves.[5]

The facial nerve is the most commonly affected cranial nerve in sarcoidosis and may be the first finding.[8] Sarcoidosis may cause facial paralysis by many mechanisms including meningeal inflammation, parotitis, spinal involvement, stroke/vasculitis or compression from intraparenchymal lesions. Although unilateral involvement is common, simultaneous or sequential bilateral involvement may also occur.[8] MRI is usually normal, but when abnormal, the most common findings are facial nerve contrast enhancement or leptomeningeal contrast enhancement.[8] Lyme disease should be excluded when bilateral facial paralysis is seen. Parotitis should be considered when facial paralysis occurs with unilateral throat or neck pain and swelling. Heerfordt Waldenström syndrome causing parotitis, facial paralysis, fever and ocular inflammation is pathognomonic for sarcoidosis.[9] NS may cause optic neuritis or peri neuritis, which may involve the optic chiasm.

Vestibulocochlear nerve involvement with vestibular dysfunction and/or hearing loss is typically associated with possible leptomeninges's at the base of the brain. Other cranial neuropathies related to NS are less common.[10]

Hypothalamic/pituitary involvement: Hypothalamic/pituitary involvement and associated neuroendocrine dysfunction is seen in 10%-25% of cases. Endocrine dysfunction most commonly includes anterior hypopituitarism (LH/FSH 89%; TSH 67%; GH 50% and ACTH 49%), hyperprolactinemia (49%) and diabetes insipidus (65%) and may be the presenting symptom of NS in approximately half of patients with sellar disease.[11] MRI findings include thickening and contrast enhancement of the pituitary gland or stalk, sometimes extending to the hypothalamus and often multifocal findings.[12]

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Spinal involvement: Spinal cord involvement may occur by different mechanisms including spinal cord parenchymal lesion, leptomeningeal involvement, extradural space infiltration, and extraspinal tissue involvement compressing the cord. Recent studies have reported that myelopathy can be observed in 19% to 26% of patients with NS.[11,13] On imaging, it may be seen as intraparenchymal T2 hyperintensities and nodular/linear contrast enhancement in the surrounding leptomeninges.[14,15] Longitudinally extensive myelitis (LETM≥3 vertebral segments) is common[14] and should be differentiated from other causes of LETM. Other MRI findings supporting the diagnosis of neurosarcoidosis include dorsal cord subpial gadolinium enhancement pattern in ≥2 spinal segments and contrast enhancement lasting >2 months despite treatment.[16] Central canal and dorsal subpial contrast enhancement creates a trident-like image on axial images, suggesting neurosarcoidosis in patients with subacute myelitis.[17] In a 2020 series, 4 main sarcoidosis myelitis patterns were defined; LETM (45%), short tumefactive myelitis (23%), meningitis/meningoradiculitis (23%), anterior myelitis adjacent to degenerative disc (10%).[18] As in the brain, mass-like spinal dural, contrasting lesions can be seen. Although cervical and thoracic involvement is more likely, involvement of the conus medullaris and cauda equina can also be seen.

Meningeal involvement: Neurosarcoidosis most commonly affects the leptomeninges (pia and arachnoid mater). If the pia or leptomeninges are involved, subacute meningitis syndrome may occur and this condition may become chronic over time. It has a preference for the skull base (basilar meningitis) and may extend to the spinal cord meninges.[5] Headache is common in patients with radiographic leptomeningeal involvement, but the presence of fever and nuchal rigidity suggestive of clinical meningitis is rarely observed.[19] Compression of the ascending nerve roots in the brain stem may cause cranial neuropathies. On MRI, leptomeningeal involvement which may also have a nodular component may be observed.

Parenchymal involvement: Parenchymal involvement of neurosarcoidosis causes symptoms specific to the involved area. Multifocal lesions are more common than solitary lesions.[20,21] It may occur as a result of meningeal dissemination or vascular involvement. Intraparenchymal mass-like lesions may occur in roughly 15% of cases and may cause seizures/focal deficits. Contrast enhancing, T2 hyperintense, T1 isointense lesions are among the characteristic MRI findings. NS-associated cerebrovascular disease may present with involvement of small, medium and large veins/venules. Venous sinus thrombosis due to vascular compression may also be seen[22], but there may be many potential causes of typical ischemic or hemorrhagic stroke in patients with known sarcoidosis and may not be directly attributable to NS.

Encephalopathy: Subcortical encephalopathy, including dementia, can be seen in neurosarcoidosis. Non-contrasting, nonspecific white matter lesions may be detected. Since they do not correlate with clinical findings in NS and do not decrease with immunosuppressive treatment, their relationship with NS is unclear and often suggests comorbid small vessel disease.[10]

Neuropsychiatric Illness: Depression and other neuropsychiatric symptoms are nonspecific and may not be directly related to NS. It has been reported that 60-66% of patients with NS develop depression and up to 20% develop other neuropsychiatric symptoms including psychosis.[7]

Peripheral Nervous System (PSS)

The PSS sarcoidosis spectrum includes polyneuropathies or polyradiculoneuropathy, which can involve both large and small fibers with pure motor, sensory or sensorimotor features, including a Guillain-Barre-like syndrome. Peripheral neuropathy is reported in approximately 15-20% of patients. Peripheral nerve vasculitis can produce mononeuritis multiplex-like involvement with axonal features. Symmetric chronic sensorimotor axonal type of peripheral neuropathy is most commonly detected by EMG. The relationship between neuropathy and sarcoidosis can be more clearly supported by biopsy. Both nerve and muscle should be examined together in biopsy. Subclinical muscle involvement is also found in 90% of nerve biopsies.[23]

Small fiber neuropathy: Small fiber neuropathy is common in systemic sarcoidosis, but its pathogenesis is unclear.[24] Therefore, it is considered as a sign of paraneurosarcoidosis in the current consensus diagnostic criteria and does not always suggest granulomatous inflammation.[25] A large 2017 study found that in approximately 25% of sarcoidosis patients with confirmed small fiber neuropathy, the neuropathy had an additional possible etiology.[24]

Myopathy: A 2018 study of 48 patients with symptomatic muscle sarcoidosis identified 4 patterns based on clinical presentation, EMG and pathology. These include nodular (27%); smoldering (29%); acute, subacute or progressive myopathic (35%); and combined myopathic and neurogenic pattern (10%). The clinical course varies depending on the phenotype.[26]

DIAGNOSIS

Diagnostic Criteria for Neurosarcoidosis

The updated consensus criteria were published in 2018 and classify cases as “definite, probable, possible” NS according to pathologic and clinical findings.[25]

Definite; 1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes.

2. The nervous system pathology is consistent with neurosarcoidosis. Type a; extraneural sarcoidosis is evident. Type b; non-extraneural sarcoidosis is evident (isolated CNS sarcoidosis).

Probable; 1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system after rigorous exclusion of other causes. 2.There is pathologic confirmation of systemic granulomatous disease consistent with sarcoidosis.

Possible; 1. The clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations and MRI, CSF, and/orEMG/NCS findings typical of granulomatous inflammation of the nervous system, and after rigorous exclusion of other causes.

2. There is no pathologic confirmation of granulomatous disease.

Serum Tests

These tests are mostly used to elucidate possible organ involvement or other possible etiology of sarcoidosis, as there is no specific or sensitive test. Acute phase reactants may be elevated but are not specific. Vitamin D hypervitaminosis and hypercalcemia may occasionally be detected and should be investigated in terms of hyperparathyroidism.[10] Serum ACE levels are found to be increased in 60% of pulmonary sarcoidosis cases.[27] A study in 2019 showed that serum dissolved IL-2 receptor levels were 88% sensitive and 85% specific in sarcoidosis, while ACE levels were 62% sensitive and 76% specific.[28]

CSF Analysis

Lumbar puncture is recommended in patients with CNS neurosarcoidosis to investigate the presence of intrathecal inflammation and to exclude other possible etiologies, especially if leptomeningeal involvement is present. Most CNS NS have abnormal results on CSF analysis, but no test is specific. Typically, increased CSF protein and mild or moderate pleocytosis (<100 cells) with lymphocyte predominance may be detected. Neutrophils may be detected, eosinophils are rare. Isolated increased CSF protein may suggest inflammation but is not specific.[10] It is one of the rare diseases that may cause hypoglycorrhachia without being infectious, but <20 mg/dl should suggest fungal, mycobacterial and malignant etiologies.[29]

Oligoclonal band (OBC) and elevated IgG index can be observed in 20-40% of neurosarcoidosis cases but are nonspecific.[30] CSF ACE level has low sensitivity and low specificity.[31] Hypoglycorrhagia and high CSF ACE levels have been found to be associated with NS in patients with LETM.[21] In a study comparing NS, MS and other inflammatory diseases, an increase in CSF CD4/CD8 and IL-6 was found in favor of neurosarcoidosis.[32] CSF IL-6 >50 pg/ml was found to be associated with NS progression or relapse.[32]

Neuroimaging

When examining suspected cases of neurosarcoidosis, MRI with or without contrast is the most appropriate imaging modality. Typical MRI may show pachy/leptomeningeal involvement, perivascular infiltration, MS-like lesions, mass-like lesions, cranial nerve infiltration, pituitary involvement.

Contrast uptake is not specific but is valuable in terms of MS neurosarcoidosis. Deep medullary vein congestion and radial perivenular involvement may be significant for NS.[33] MRI has a role in response to treatment and clinical decision making.

Systemic Evaluation

Early diagnostic goals in neurosarcoidosis include looking for findings in favor of systemic sarcoidosis to support the diagnosis. A detailed physical examination is essential in systemic evaluation. Eye and fundus examination is necessary for ocular involvement. In roughly half of patients with CNS neurosarcoidosis, abnormalities are found on chest radiography (PAAG).[34,35] When clinical suspicion for sarcoidosis is high and PAAG is normal, thoracic, abdominal and pelvic CT may be valuable in determining sarcoidosis.

When structural imaging does not reveal target tissue for biopsy, combined fluorodeoxyglucose PET (FDG-PET)/CT may reveal metabolically active lymph nodes or other occult lesions that may appear normal on CT.[36] FDG-PET can also show metabolically active lesions in the brain or spinal cord, but these are almost always better seen on MRI.

Biopsy

Meningeal, brain or spinal cord biopsy is sometimes indicated if the diagnosis remains suspicious. Extra neural tissue biopsy from other clinically affected organs is generally preferred when possible as it is less risky; skin, lymph node, and lung (transbronchial) biopsies may provide high yield.[34,35] Muscle and peripheral nerve biopsy, including quantitative nerve terminal analysis to document small fiber sensory neuropathy[37] and epidermal biopsy including sweat gland innervation, can all be easily performed for the appropriate syndrome. In the absence of a defined systemic disease, a central or peripheral nervous system biopsy should be considered instead of empiric therapy to establish the diagnosis. Biopsy to reveal an alternative neurologic diagnosis should also be considered for patients with known systemic sarcoidosis and neurologic disease who progressively deteriorate despite treatment.[38] Sarcoid granulomas are not histologically different from other granulomas and related granulomas require exclusion of acid-fast bacilli and fungi with special stains and infectious processes with cultures.

TREATMENT

The aim of disease-modifying therapy is to prevent or minimize damage to organs from granulomatous inflammation. Immunosuppressive therapy may not be required in mild disease. However, in cases with CNS neurosarcoidosis and peripheral thick nerve fiber involvement, early immunosuppressive therapy is recommended to reduce neurological damage and disability. A multidisciplinary approach is required in multisystem involvement. No randomized trials are yet available to guide NS treatment; therefore, treatment is based on expert opinion and observations from case series and single reports.[10]

Glucocorticoids

Glucocorticoids are the first-line agents in the treatment of neurosarcoidosis and the dose and duration of treatment should be determined according to the severity of the disease and response to treatment; they act rapidly in most patients.[7,35]

Patients with severe symptoms may be treated with a dose of 1 g IV methylprednisolone daily for 3-5 days followed by a tapered course of oral glucocorticoids. In milder cases, bioequivalent doses of 0.5-1 mg/kg/day prednisone or other glucocorticoid formulations may be effective. For patients with mild or moderate symptoms, monotherapy with prednisone

may be adequate and prednisone can be gradually tapered over several months when clinical and imaging response is adequate. When tapering glucocorticoids in NS, care should be taken to consider and evaluate relapse or worsening. Early switch to steroid-sparing therapy may be considered in cases of safety and toxicity concerns with glucocorticoids. Given the frequent recurrence of disease activity when steroids are discontinued, close clinical and radiologic follow-up is important during glucocorticoid taper.

Steroid Sparing Agents

Patients whose condition worsens despite aggressive glucocorticoid therapy, who cannot tolerate glucocorticoids, or who have a primary contraindication to glucocorticoid therapy may benefit from alternative therapies.[4,39,40] Expert opinion suggests that alternative therapies should be considered early in treatment for patients receiving high-dose glucocorticoid therapy and in whom symptoms such as parenchymal inflammation, hydrocephalus or optic neuropathy are likely to require long-term treatment.

There are no prospective studies comparing various alternative therapies in patients with neurosarcoidosis. The decision on the specific agent should be based on ease of use, cost and avoidance of complications of a particular drug. A number of steroid sparing agents have been used in the treatment of NS, including azathioprine, methotrexate, mycophenolate mofetil, hydroxychloroquine, cyclophosphamide and TNF inhibitors.[10] In a small case series, mycophenolate mofetil was effective in the treatment of diseases affecting the central nervous system (CNS) but not in sarcoid myopathy.[41] A retrospective multicenter study showed that relapse in patients with neurosarcoidosis methotrexate and mycophenolate mofetil in prevention.[42] Methotrexate treatment was associated with 0.2 relapses per year, while mycophenolate mofetil was associated with 0.6 relapses per year, and adverse effects were found to be more common with methotrexate than with mycophenolate mofetil. It may take several months for agents such as azathioprine, methotrexate and mycophenolate mofetil to achieve full clinical immunosuppressive effect, during which time it may be beneficial to continue oral glucocorticoids. The patient's response to any specific drug cannot be predicted and two or three agents should be tried before concluding that the patient's disease is resistant.[10]

TNF Inhibitors

The best-studied TNF-alpha antagonist in NS is infliximab, a chimeric monoclonal antibody against TNF-alpha that appears to be able to inhibit granuloma formation and induce complement- and cell-mediated apoptosis in sarcoidosis. Observational studies suggest that infliximab may be useful in selected patients with pulmonary and extrapulmonary sarcoidosis refractory to glucocorticoid therapy.[43-49] In a series of seven patients with glucocorticoid-resistant neurosarcoidosis, infliximab treatment was associated with symptom relief, regression of neurologic deficits and reduction in disease activity on MRI.[50] The use of infliximab requires an initial intravenous infusion (5 mg/kg ideal body weight) and is then administered periodically as the clinical course progresses.

Adalimumab is an injectable TNF-alpha antagonist that may be effective in the treatment of small fiber neuropathy.[51,52]

B Cell Targeted Therapy

Rituximab is thought to be effective in systemic sarcoidosis and possible neurosarcoidosis.[53]

For patients with refractory disease, treatment with other novel agents may be considered. In these patients, tocilizumab (interleukin 6 IL_6 receptor antagonist) and tofacitinib (a JAK inhibitor) have been used.[54,55] Tofacitinib has been favorable for treatment-resistant cutaneous sarcoidosis. Clinical improvement has also been observed with tocilizumab in treatment-resistant sarcoidosis with lung, sinus and cutaneous involvement. Since small fiber neuropathy typically does not respond to conventional immunosuppressive drug therapy, adalimumab or intravenous immune globulin (IVIG) therapies are frequently used in the treatment of small fiber sensory or autonomic neuropathy.[24,56] Cranial or spinal radiotherapy has been used for refractory disease and should be considered when patients have failed glucocorticoid therapy and at least two trials of alternative agents.[57] It is also occasionally needed for patients with acute, life-threatening disease. Immunosuppression usually persists during radiation therapy, albeit at less intense levels.

PROGNOSIS

The goal of immunosuppression in NS is to minimize the risk of neurological damage from granulomatous inflammation. In many patients, the goal is complete elimination of the neuroinflammatory response. In others, suppression of the inflammatory response, even without complete remission, is the appropriate balance of therapeutic risk. Treatment response is assessed by anamnesis, examination and neuroimaging studies.

In a patient who is clinically well and has abnormal MRI findings attributable to NS, a reasonable approach is to repeat imaging 2-4 months after initiation of treatment. The frequency of MRI monitoring can then be gradually spaced over time depending on treatment response.

When there are no abnormal findings on MRI, MRI changes of unknown etiology, or discordance between clinical symptoms and MRI findings, it may be clinically useful to repeat CSF examination to monitor disease activity and confirm remission. The clinical response may lag behind the MRI response; if there is damage from the underlying inflammatory process, the neurological impairment may not necessarily improve, but should not worsen. Although the disease may regress and some patients may discontinue treatment, there is a risk of recurrence with discontinuation.

CONCLUSION

Recent advances in the diagnosis and treatment of neurosarcoidosis suggest updated diagnostic criteria and an important role for TNF-alpha inhibitors in aggressive and/or refractory cases. Optimal treatment strategies need randomised clinical trials.

ETHICAL DECLARATIONS

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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